Trientine tetrahydrochloride

(Cuprior)

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BASL
British Association for the Study of the Liver

Cuprior 150 mg film-coated tablets

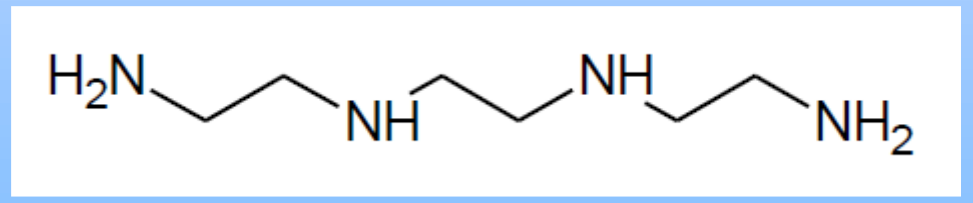
gmporphan
drugs for orphan diseases

Triethylenetetramine tetrahydrochloride (trientine tetrahydrochloride; Cuprior™)

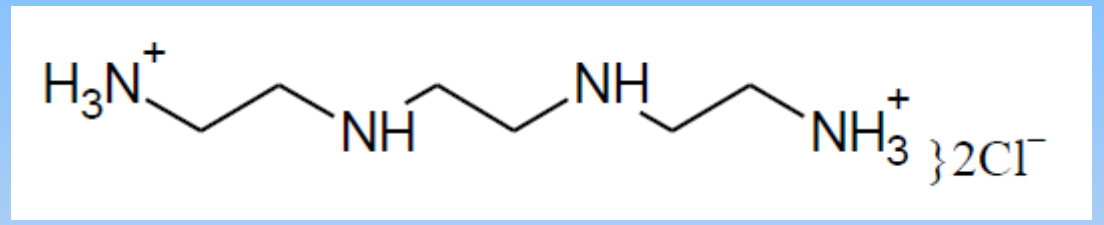
- First reported in 1920
- Crystalline solid mp 266-270 °C
- Prepared by addition of HCl to triethylenetetramine
- Not reported to be hygroscopic
- Cu^{2+} coordination noted in 1936

Trientine (triethylenetetramine) structures

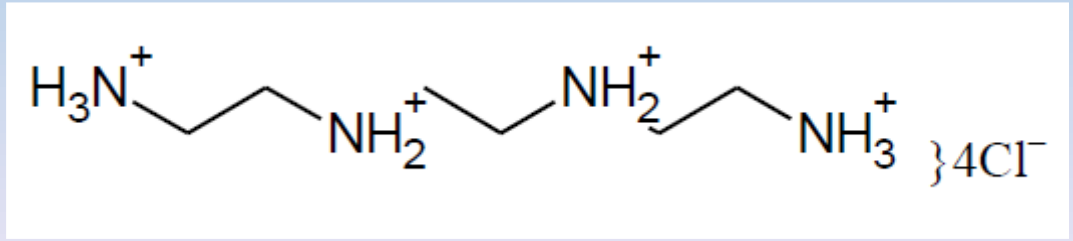
trientine free base (Tosoh, Japan)*
cost (technical grade): ~ 0.0006p/mg



Cufence (Univar: trientine.2HCl)
200 mg free base/capsule
cost/capsule: 15p/mg (free base)



Cuprior (GMP-Orphan: trientine.4HCl)
150 mg free base/tablet
cost/tablet: 25p/mg (free base)



*Quotation from Henan Tianfu Chemical Co., China

Cuprior 150 mg tablets

- Stable at room temperature; do not require refrigeration
- 16 mm x 8 mm – each tablet dividable into equal doses
- Recommended adult dose: 3–6½ tablets/day
- 6 x Cuprior tablets/day ≡ 0.9 grams chloride ion

  [Dietary chloride ion intake = 2 grams/day]

Cuprior: 150 mg base ≡ 300 mg trientine.4HCl; Cufence: 200 mg base ≡ 300 mg trientine.2HCl

GMP-Orphan – EMA submission data (2015)

Cuprior tablets compared with Cufence capsules

Dissolution

- Faster aqueous dissolution (pH 1.2; pH 4.0 and pH 6.8)
- Ascribed to differences in formulation rather than solubility differences between the two salts

Bioavailablity

- Higher bioavailability *cf.* Cufence (pharmacokinetic data)
- Approx. 60% dose adjustment factor proposed to provide daily dose of trientine free base equivalent to that from the dihydrochloride

Bioavailability of Cuprior and Cufence

Relative bioavailabilities determined by:

- Aqueous solubility and dissolution
- Protonation of trientine base (bis-protonated at pH 6-7; tetra-protonated at pH 2-3)
- pH of gastric acid (pH 1.5 to 3.5)
- pH of intestinal tract (pH 6 to 7.4)

Bioavailability of Cuprior and Cufence

Conclusions:

- The speciation of trientine *in vivo* will be the same irrespective of the administration of the dihydrochloride or the tetrahydrochloride
- Once in the intestinal tract, the subsequent absorption, distribution and metabolism of the two drugs will also be equivalent

Therefore:

Relative bioavailability of trientine is determined by aqueous solubility/dissolution of the formulated salt

Cuprior: clinical trial

Trientine tetrahydrochloride (TETA.4HCl) for the treatment of Wilson's disease

- ClinicalTrials.gov Identifier: NCT03539952
- Participating countries: Belgium, Brazil, Denmark, France, Germany, Italy, Poland, Sweden, UK and USA
- Completion date: November 2021

https://www.clinicaltrials.gov/ct2/show/NCT03539952